

INTENDED USE

The LATEX-CRYPTOCOCCUS ANTIGEN TEST is a simple and rapid latex agglutination test for the qualitative or semi-quantitative detection of the capsular polysaccharide antigens of *Cryptococcus neoformans* in serum and cerebrospinal fluid (CSF) as an aid in the diagnosis of Cryptococcosis.

SUMMARY and EXPLANATION of the Test

Cryptococcosis is caused by the encapsulated yeast *Cryptococcus neoformans*. Individuals with impaired cell-mediated immune (CMI) function due to acquired immunodeficiency syndrome (AIDS) (39), lymphoproliferative disorders (38), steroid therapy (13), and organ transplantation (12) are at increased risk of Cryptococcosis. AIDS accounts for 80-90% of Cryptococcal infections (24) where Cryptococcosis occurs in 5-10% of AIDS patients in the United States (24). The incidence of Cryptococcosis in other parts of the world, such as Africa, is as high as 30% (8). Cryptococcosis is the fourth most common opportunistic, life-threatening infection among AIDS patients (23).

The LATEX-CRYPTOCOCCUS ANTIGEN TEST is a simple, sensitive test capable of detecting *C. neoformans* polysaccharide antigens in serum and CSF (1), and is superior in sensitivity to the India ink mount (4,6). Clinical studies established the prognostic value of the test (9,16,21,22) and showed it to be a valuable aid in establishing a diagnosis when the culture was negative (14). *C. neoformans* antigens were present in both serum and CSF in 86% of 330 confirmed cases of Cryptococcal meningitis (22). Antigen was detected in CSF specimens in 99% of these 330 cases but in only 87% of serum samples alone (22). Paired serum and CSF specimens allowed detection of the antigen in each confirmed case (22). Parallel serologic studies for both antigen (REF CR1003 & CR1004) and antibody (REF YA1001) are recommended to insure detection of extrameningeal Cryptococcosis (22).

BIOLOGICAL PRINCIPLES

The LATEX-CRYPTOCOCCUS ANTIGEN TEST is based upon the principle that anti-Cryptococcal antibody-coated latex particles will agglutinate with specimens containing Cryptococcal capsular polysaccharide antigens (4,6). Previously, the detection of this antigen in serum was hampered by the presence of rheumatoid factor (3,15). Pretreatment of serum specimens with Pronase (REF DE0010) reduces nonspecific interference and enhances the detection of capsular polysaccharide antigens of *C. neoformans* (17) due to rheumatoid factor (34) and immune complexes (33).

MATERIALS PROVIDED

- A. Specimen Diluent** (10 ml, REF GB0020): Concentrated (10X) glycine buffered saline (pH 8.6) containing albumin and a preservative.
- B. Cryptococcal Latex:** (1.5 ml, REF CG0020 or 3.5 ml, REF CG0010): Standardized latex particles sensitized with rabbit anti-cryptococcal globulin in glycine buffered saline containing a preservative. DO NOT FREEZE.
- C. Cryptococcal Antigen Positive Control** (1 ml, REF CB0010): Purified capsular polysaccharide antigens containing a preservative.
- D. Negative Control** (1 ml, REF N80110): Normal goat serum containing a preservative.
- E. Pronase** (1.75 ml, REF DE0010): Lyophilized Pronase containing a preservative.
- F. Pronase Control** (2 ml, REF R20000): Goat anti-rabbit globulin containing a preservative.
- G. Pronase Inhibitor** (6 ml, REF EI0010): Contains an inhibitor for the Pronase.
- H. Disposable Ring Slides** (REF SC0020)
- I. Package Insert**

MATERIALS NOT PROVIDED

1. Distilled or DI water
2. 1-ml serological pipettes
3. Disposable borosilicate glass test tubes (non-siliconized), 10 or 12 X 75 mm, for specimen dilutions & pronase aliquots
4. Test tube rack
5. Waterbath or heat block (56 °C)
6. Wooden applicator sticks
7. Rotator set to 100 rpm
8. Timer
9. Pipettor (25-µl and 100-µl)

PRECAUTIONS

1. All reagents are intended for *in vitro* diagnostic use only!
2. Specific standardization is necessary to produce our high quality reagents and materials. IMMY cannot guarantee the performance of its products when used with materials purchased from other manufacturers.

3. Do not use reagents containing foreign matter, particulates or aggregates, which indicate contamination or improper storage or handling.
4. Specimens must not contain bacteria, visible lipids, or other obvious signs of contamination.
5. NEVER heat-inactivate Pronase Control as this could cause aberrant control reactions.
6. Do not store specimens in a frost-free type freezer. Repeated freezing and thawing of the specimens can affect test results.
7. Do not store rehydrated Pronase in a frost-free type freezer.
8. Care should be taken not to introduce syneresis fluid, which is present in various types of agar, into any specimens prior to testing as this may cause spurious results.
9. When handling patient specimens, adequate measures should be taken to prevent exposure to etiologic agents potentially present in the specimen.
10. reagents are preserved with sodium azide [0.095% (w/w)], which is a skin irritant. Avoid skin contact with the kit components. Do not mix reagents with acid as this may result in the formation of hydrazoic acid, an extremely toxic gas. Additionally, disposal of reagents containing sodium azide into lead or copper plumbing can result in the formation of explosive metal azides. It is therefore recommended that excess reagents simply be discarded in an appropriate waste receptacle.
11. GB0020 contains Sodium Azide. WARNING. Harmful if swallowed. Wash thoroughly after handling. Do not eat, drink, or smoke when using this product. IF SWALLOWED: Call a POISON CENTER or doctor/physician if you feel unwell. Dispose of contents/container in accordance to local, regional, national, and/or international regulations.
12. DE0010 contains Pronase. DANGER. Cause skin irritation. Causes serious eye irritation. May cause allergy or asthma symptoms or breathing difficulties if inhaled. May cause respiratory irritation. Precautionary Statements: Avoid breathing dust/fume/gas mist/ vapors/spray. Wash skin thoroughly after handling. Use only outdoors or in a well-ventilated area. Wear protective gloves/protective clothing/eye protection/face protection. In case of inadequate ventilation wear respiratory protection. IF ON SKIN: Wash with plenty of soap and water. IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing. IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. If skin irritation occurs: Get medical advice/attention. If eye irritation persists: Get medical advice/attention. If experiencing respiratory symptoms: Call a POISON CENTER or doctor/physician. Take off contaminated clothing and wash before reuse. Store in a well-ventilated place. Keep container tightly closed. Store locked up. Dispose of contents/container in accordance to local, regional, national, and/or international regulations.
13. GB0020 and DE0010 must be stored in kit box bearing complete label containing elements as defined in 29 CFR 1910.1200 (f)(1)



STABILITY AND STORAGE

All reagents (except Pronase after rehydration, which must be frozen at -20°C or colder) should be stored at 2-8°C. Prolonged periods at room temperature should be avoided. Avoid FREEZING latex suspensions as this causes granularity, which might be interpreted as a false positive reaction. The frozen aliquots of Pronase may continue to be used as long as they continue to destroy the activity of the Pronase Control in monthly tests and are within the expiration dating.

REAGENT PREPARATION

Reconstitute or dilute the following reagents with the indicated volume of distilled or DI water:

- A. Pronase** (REF DE0010) 1.75 ml; Reconstituted Pronase should be aliquoted into test tubes in 0.05 ml (50 µl) amounts, sealed, and frozen immediately at -20°C or colder. Do NOT use siliconized tubes.
- B. Specimen Diluent** (REF GB0020) Dilute 1:10
- C. Latex solutions** must appear as homogeneous suspensions.
- D.** When using the negative control (REF N80110) for the first time, heat inactivate at 56°C for 30 minutes.
- E.** The ring slides (REF SC0020) should be discarded after each use.

SPECIMEN PREPARATION

- A. Cerebrospinal fluid (CSF)**
1. Collect specimen aseptically following accepted

- procedures.
2. Centrifuge at 1000 x g for 15 minutes to ensure the removal of all white cells and particulate matter.
3. Carefully aspirate the CSF into a sterile container and seal.
4. Specimen may be processed immediately, refrigerated, preserved by freezing at -20°C or by adding thimerosal to provide a final concentration of 0.01%.
5. Incubate CSF specimen at 100°C for 5 minutes.
6. Specimen is ready for testing (see **PROCEDURE**).

B. Serum

1. Collect whole blood aseptically following accepted procedures. The specimen must not contain anticoagulants as this will invalidate the test.
2. Permit blood to clot for 10 minutes or more at room temperature in a collection tube.
3. Centrifuge 1000 x g for 15 minutes
4. Carefully aspirate the serum into a sterile container and seal.
5. Specimen may be processed immediately, refrigerated, preserved by freezing at -20°C or by adding thimerosal to provide a final concentration of 0.01%.
6. Add 300 µl of serum to 50 µl aliquot of Pronase (REF DE0010) and seal tube with parafilm.
7. Incubate serum/Pronase solution at 56°C for 30 minutes.
8. Add 1 drop of Pronase Inhibitor (REF EI0010) and mix to terminate enzymatic digestion.
9. Specimen is ready for testing (see **PROCEDURE**).

PROCEDURE

Screening Procedure:

1. Add 25 µl of Cryptococcus Antigen Positive Control (REF CB0010), Negative Control (REF N80110) and each heat-treated CSF and/or Pronase-treated serum specimen onto separate rings of the ring slide. Use a new pipette tip for each reagent and specimen.
2. Add 25 µl of Cryptococcal Latex (REF CG0020 or CG0010) to each ring.
3. Using separate applicator sticks, thoroughly mix the contents of each ring.
4. Rotate by hand or place the ring slide on a rotator set to 100 rpm (+/- 25) for 5 minutes at room temperature.
5. Read the reactions immediately (see **Reading the Test**).

Titration Procedure:

- Patient specimens showing a 1+ or greater reaction should be titrated.
1. Add 100 µl of Specimen Diluent (REF GB0020) to each of 10 tubes labeled 1-10 and place in a rack (1:2 through 1:1024). Additional dilutions may be necessary if the specimen is positive at 1:1024.
 2. Add 100 µl of patient specimen to tube #1 and mix well.
 3. Transfer 100 µl from tube #1 to tube #2 and mix well. Continue this dilution procedure through tube #10.
 4. Add 25 µl of Cryptococcus Antigen Positive Control (REF CB0010), Negative Control (REF N80110) and each specimen dilution onto separate rings of the ring slide.
 5. Add 25 µl of Cryptococcal Latex (REF CG0020 or CG0010) to each ring.
 6. Using separate applicator sticks, thoroughly mix the contents of each ring.
 7. Rotate by hand or place the ring slide on a rotator set to 100 rpm (+/- 25) for 5 minutes at room temperature.
 8. Read the reactions immediately (see **Reading the Test**).

Reading the Test:

Read the reactions immediately over a dark background and rate them on a scale from negative to 4+. Do Not Magnify. For comparison, the Cryptococcus Antigen Positive Control should give a 2+ or greater reaction and the Negative Control should be less than 1+ (see Reference Reaction Pictures). The graduations of the reaction strengths are as follows: **Negative (-):** a homogeneous suspension of particles with no visible clumping. **One Plus (1+):** fine granulation against a milky background. **Two Plus (2+):** small but definite clumps against a slightly cloudy background. **Three Plus (3+):** large and small clumps against a clear background. **Four Plus (4+):** large clumps against a very clear background.

QUALITY CONTROL

Latex Control: Periodically, the sensitivity of the Cryptococcal Latex reagent (REF CG0020 or CG0010) may be tested by titrating the Cryptococcal Antigen Positive Control (REF CB0010). The Cryptococcal Antigen Positive Control should titer 1:4 ± 1 dilution if the sensitivity of the Cryptococcal Latex reagent is satisfactory.

Pronase Control:

At least once monthly, a frozen aliquote of Pronase (REF DE0010) should be tested for proteolytic activity by substituting a 300 µl aliquote of Pronase Control (REF R20000) for specimen in steps 6-9 in serum specimen preparation. Both the Pronase-treated sample of Pronase Control and an untreated sample of Pronase Control should be tested simultaneously using the **Screening Procedure** above. The untreated Pronase Control must be 2+ or greater and the Pronase-treated Pronase Control must be less than 1+ (**NOTE:** The Pronase-treated Pronase Control reactions may be slightly rough, but should be less than a 1+ reaction). If the Pronase-treated Pronase Control is greater than 1+, then the proteolytic activity of Pronase has diminished and a new vial of Pronase should be rehydrated, aliquoted, frozen, and tested.

INTERPRETATION OF RESULTS

Control Reactions:

The Cryptococcal Antigen Positive Control must be 2+ or greater, and the Negative Control must be less than 1+ with the Cryptococcal Latex. If either control is incorrect, one or both of the reagents is unsatisfactory (or the tests were performed improperly) and any patient tests with the reagents are invalid. A positive reaction with the Negative Control may indicate possible contamination or freezing of the Cryptococcal Latex, which could produce false positive results in patient specimens. The Pronase Control detects the presence of rabbit globulin on the latex particles. Failure of the Pronase Control to give a positive reaction indicates that one of the reagents is unsatisfactory.

Patient Specimens:

- A. **Negative:** If the screening test performed on the undiluted patient specimen was negative or a 1 + reaction, then the test should be reported as negative. However, 1 + reactions may be suggestive of Cryptococcosis (22). If the clinical symptoms of the patient are suggestive of Cryptococcosis, subsequent specimens and culture are strongly recommended. Weakly reactive specimens (e.g. 1+) should be checked for prozone effect of high titers by testing using the **Titration Procedure** (29,32). If prozoning is suspected, repeat the test with both a 1:10 and a 1:100 dilution of the specimen.
- B. **Positive:** If a 2+ or greater reaction is observed in the **Screening Procedure**, then the specimen is titrated using the **Titration Procedure**. The titer is reported as the highest dilution showing a 2+ or greater reaction.

LIMITATIONS OF THE PROCEDURE

A negative test does not exclude the possibility of cryptococcal infection, particularly when a single patient specimen has been tested and the patient has symptoms consistent with Cryptococcosis (1). False-negative reactions may be caused by low titers, early infection, presence of immune complexes (30), prozone effect of high titers (32), or poorly encapsulated strains with low production of polysaccharide (28). False-positive reactions can occur due to the presence of rheumatoid factor (3,19), agar syneresis fluid (7,11,20), *Capsulophaga animorsus* (36), *Trichosporon beigellii* (25), hydroxyethyl starch (26), sera with >200 mg Fe³⁺/dL (10), improper cleaning of the ring slide (5), and non-specific reactivity in HIV-infected patients (37). Pronase treatment has been shown to reduce false positives (17), increase titers (17,18), and increase sensitivity (35) in serum specimens.

EXPECTED VALUES AND SPECIFIC PERFORMANCE CHARACTERISTICS

The latex agglutination test for *C. neoformans* antigens has both diagnostic and prognostic value (29). A positive reaction in serum or CSF of an untreated patient at titers of 1:4 or less is highly suggestive of Cryptococcal infection (29). Titers of 1:8 or greater usually indicate active Cryptococcosis (29). The antigen titer is usually proportional to the extent of infection, with increasing titers reflecting progressive infection and a poor prognosis (29). Declining titers indicates a positive response to therapy in the treated patient (1,29). Failure of titers to decline indicates inadequate therapy (29). Occasionally, however, low titers may persist for an indefinite period in the presence of nonviable fungus and clinical improvement (1,29). When antigen titration is being used to monitor therapy, all titrations should be performed with the same manufacturer's kit. It is also good practice to titer serial specimens simultaneously to minimize laboratory variation.

Patients with extrameningeal Cryptococcosis have positive tests with the LATEX-CRYPTOCOCCUS ANTIGEN DETECTION SYSTEM or the YA-CRYPTOCOCCUS ANTIBODY DETECTION SYSTEM tests approximately 97% of the time (22). Therefore, the concomitant use of antigen (REF CR1003 & CR1004) and antibody (REF YA1001) tests is recommended (22). Antibody tests are positive in early stages of Cryptococcosis, those with localized lesions, and/or if therapy has been successfully administered (22).

The sensitivity and specificity for the LATEX - CRYPTOCOCCUS test has been reported to be 93-100% and 93-100%, respectively (31,35). The lower detection limits for polysaccharide antigens from different serotypes of *C. neoformans* were determined by spiking serum with known concentrations of purified antigens (27). Serotype A antigen was detected at a level of 0.5 ng/ml; serotype B antigen was detected at 0.5 ng/ml; serotype C antigen was

detected at 25 ng/ml; and serotype D antigen was detected at 0.5 ng/ml (2).

REFERENCES

1. **D. Palmer, L. Kaufman, W. Kaplan, and J. Cavallaro (eds.)** 1977. Slide Latex Agglutination test for Cryptococcal Antigen, p. 94-106. Serodiagnosis of Mycotic Diseases. CC Thomas, Springfield, IL.
2. **Baumann, S. K.** Unpublished Data. 2002.
3. **Bennett, J. E. and J. W. Bailey.** 1971. Control for rheumatoid factor in the latex test for cryptococcosis. *Am.J.Clin.Pathol.* 56:360-365.
4. **Bennett, J. E., H. F. Hasenclever, and B. S. Tynes.** 1964. Detection of Cryptococcal polysaccharide in serum and spinal fluid: Value in diagnosis and prognosis. *Trans.Assoc.Am.Physicians* 77:145-150.
5. **Blevins, L. B., J. Fenn, H. Segal, P. Newcomb-Gayman, and K. C. Carroll.** 1995. False-positive cryptococcal antigen latex agglutination caused by disinfectants and soaps. *J.Clin.Microbiol.* 33:1674-1675.
6. **Bloomfield, N., M. A. Gordon, and F. Elmenforf.** 1963. Detection of Cryptococcus neoformans Antigen in Body Fluids by Latex Particle Agglutination. *Proc.Soc.Exp.Biol.Med.* 114:64-67.
7. **Boom, W. H., D. J. Piper, K. L. Ruoff, and M. J. Ferraro.** 1985. New cause for false-positive results with the cryptococcal antigen test by latex agglutination. *J.Clin.Microbiol.* 22:856-857.
8. **Clumeck, N., J. Sonnet, H. Taelman, F. Mascart-Lemone, M. De Bruyere, P. Vandepierre, J. Dasnoy, L. Marcelis, M. Lamy, and C. Jonas.** 1984. Acquired immunodeficiency syndrome in African patients. *N.Engl.J.Med.* 310:492-497.
9. **Diamond, R. D. and J. E. Bennett.** 1974. Prognostic factors in cryptococcal meningitis. A study in 111 cases. *Ann.Intern.Med.* 80:176-181.
10. **Eberhard, T. H.** 1993. False-positive reactions in cryptococcal antigen determination. *Am.J.Clin.Pathol.* 100:364.
11. **Engler, H. D. and Y. R. Shea.** 1994. Effect of potential interference factors on performance of enzyme immunoassay and latex agglutination assay for cryptococcal antigen. *J.Clin.Microbiol.* 32:2307-2308.
12. **Gallis, H.A., R. A. Berman, T. R. Cate, J. D. Hamilton, J., C. Gunnells, and D. L. Stickel.** 1975. Fungal infection following renal transplantation. *Arch.Intern.Med.* 135:1163-1172.
13. **Goldstein, E. and O. N. Rombo.** 1962. Cryptococcal infection following steroid therapy. *Ann Intern Med* 56:114.
14. **Goodman, J. S., L. Kaufman, and M. G. Koenig.** 1971. Diagnosis of cryptococcal meningitis. Value of immunologic detection of cryptococcal antigen. *N.Engl.J.Med.* 285:434-436.
15. **Gordon, M. A. and E. W. Lapa.** 1974. Elimination of rheumatoid factor in the latex test for cryptococcosis. *Am.J.Clin.Pathol.* 61:488-494.
16. **Gordon, M. A. and D. K. Vedder.** 1966. Serologic tests in diagnosis and prognosis of cryptococcosis. *JAMA* 197:961-967.
17. **Gray, L. D. and G. D. Roberts.** 1988. Experience with the use of pronase to eliminate interference factors in the latex agglutination test for cryptococcal antigen. *J.Clin.Microbiol.* 26:2450-2451.
18. **Hamilton, J. R., A. Noble, D. W. Denning, and D. A. Stevens.** 1991. Performance of cryptococcus antigen latex agglutination kits on serum and cerebrospinal fluid specimens of AIDS patients before and after pronase treatment. *J.Clin.Microbiol.* 29:333-339.
19. **Hay, R. J. and D. W. MacKenzie.** 1982. False positive latex tests for cryptococcal antigen in cerebrospinal fluid. *J.Clin.Pathol.* 35:244-245.
20. **Heelan, J. S., L. Corpus, and N. Kessimian.** 1991. False-positive reactions in the latex agglutination test for Cryptococcus neoformans antigen. *J.Clin.Microbiol.* 29: 1260-1 261.
21. **Kaufman, L. and S. Blumer.** 1968. Value and interpretation of serological tests for the diagnosis of cryptococcosis. *Appl.Microbiol.* 16:1907-1912.
22. **Kaufman, L. and S. Blumer.** 1977. Cryptococcosis: The Awakening Giant. *Proc.4th Intl.Conf on the Mycosis.Pan Amer.Hlth.Organ., Sci.Pub.*356 176-1 82.
23. **Kovacs, J. A., A. A. Kovacs, M. Polis, W. C. Wright, V. J. Gill, C. U. Tuazon, E. P. Gelmann, H. C. Lane, R. Longfield, and G. Overturf.** 1985. Cryptococcosis in the acquired immunodeficiency syndrome. *Ann.Intern.Med.* 103:533-538.
24. **Kozel, T. R.** 1995. Virulence factors of Cryptococcus neoformans. *Trends Microbiol.* 3:295-299.
25. **McManus, E. J. and J. M. Jones.** 1985. Detection of a *Trichosporon beigellii* antigen cross-reactive with Cryptococcus neoformans capsular polysaccharide in serum from a patient with disseminated *Trichosporon* infection. *J.Clin.Microbiol.* 21:681-685.
26. **Millon, L., T. Barale, M. C. Julliot, J. Martinez, and G. Mantion.** 1995. Interference by hydroxyethyl starch used for vascular filling in latex agglutination test for cryptococcal antigen. *J.Clin.Microbiol.* 33:1917-1919.
27. **Murphy, J. W.** Supplied purified cryptococcal polysaccharide, serotypes A, B, C, and D, for use in spiking normal serum with known amounts of antigen. 2002.

28. **Perfect, J. R. and A. Casadevall.** 2002. Cryptococcosis. *Infect.Dis.Clin.NorthAm.* 16:837-8vi.
29. **Reiss, E., L. Kaufman, J. Kovacs, and M. Lindsley.** 2002. *Clinical Immunomycology*, p. 559-583. In N. Rose, R. Hamilton, and B. Detrick (eds.), *Manual of Clinical Laboratory Immunology*. ASM Press, Washington, DC.
30. **Sadamoto, S., R. Ikeda, A. Nishikawa, and T. Shinoda.** 1993. Evidence for interference by immune complexes in the serodiagnosis of cryptococcosis. *Microbiol. Immunol.* 37: 129-133.
31. **Sekhon, A. S., Garg, A. K., Kaufman, L., Kobayashi, G., Moledina, N., Notenboom, R. H., and Hamir, Z.** Multicentre Evaluation of the Latex Agglutination (LA) and Premier EIA Tests for Cryptococcal Antigen (CrAg) Detection. *Conjoint Meeting on Infectious Disease* . 1992.
32. **Stamm, A. M. and S. S. Polt.** 1980. False-negative cryptococcal antigen test. *JAMA* 244:1359.
33. **Steindl, F., C. Armbruster, K. Pierer, M. Purtscher, and H. W. Katinger.** 1998. A simple and robust method for the complete dissociation of HIV-1 p24 and other antigens from immune complexes in serum and plasma samples. *J.Immunol.Methods* 217:143-151.
34. **Stockman, L. and G. D. Roberts.** 1983. Corrected Version: Specificity of the latex test for Cryptococcal antigen: a rapid, simple method for eliminating interference factors. *J.Clin.Microbiol.* 17:945-947.
35. **Tanner, D. C., M. P. Weinstein, B. Fedorciw, K. L. Joho, J. J. Thorpe, and L. Reller.** 1994. Comparison of commercial kits for detection of cryptococcal antigen. *J.Clin.Microbiol.* 32:1680-1 684.
36. **Westerink, M. A., D. Amsterdam, R. J. Petell, M. N. Stram, and M. A. Apicella.** 1987. Septicemia due to DF-2. Cause of a false-positive cryptococcal latex agglutination result. *Am.J.Med.* 83:155-1 58.
37. **Whittier, S., R. L. Hopper, and P. Gilligan.** 1994. Elimination of false-positive serum reactivity in latex agglutination test for cryptococcal antigen in human immunodeficiency virus-infected population. *J.Clin.Microbiol.* 32:2158-2161.
38. **Zimmerman, L. E. and H. Rappaport.** 1954. Occurrence of cryptococcosis in patients with malignant disease of reticuloendothelial system. *Am.J.Clin.Pathol.* 24:1050.
39. **Zuger, A., E. Louie, R. S. Holzman, M. S. Simberkoff, and J. J. Rahal.** 1986. Cryptococcal disease in patients with the acquired immunodeficiency syndrome. Diagnostic features and outcome of treatment. *Ann Intern Med* 104:234-240.



IMMY, Inc.
2701 Corporate Centre Dr
Norman OK 73069 U.S.A.
(405)360-4669 / (800)654-3639
Fax: (405) 364-1058
Email: info@immy.com
www.immy.com



MDSS
Schiffgraben 41
30175 Hannover, Germany

International Symbol Usage

	Storage 2 - 8 C		Lot Number
	Manufactured by		Reference Number
	Expiration Date		In Vitro Diagnostics
	Conforms to European Union Requirements		Sufficient for "#" Tests

Rev. 12-05-2018

Revision 1